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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,234	06/04/2001	Ernesto Palazzini	9457-023	4468

20583 7590 09/09/2003

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	16

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,234	PALAZZINI ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,27 and 29-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,27 and 29-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's Response dated June 17, 2003

1. In the Response filed June 17, 2003, applicant presented arguments directed to the rejection of claims 26-27 and 29-36 under 35 U.S.C. 103(a). Claims 26-27 and 29-36 are pending. An action on the merits of claims 26-27 and 29-36 is contained herein below.

2. The rejection of claims 26-27 and 29-36 under 35 U.S.C § 103(a), is maintained for the reasons of record set forth in the Office Action dated December 17, 2002.

Rejections of Record Set Forth in Office Action dated December 17, 2002

3. The rejection of claims 26-27 under 35 U.S.C. 103(a) was maintained for the reasons of record set forth in the Office Action dated June 27, 2002.

4. Claims 29-36 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Baggio et al. US 5,686,432 (Baggio), Cristofori et al. US 5,252,339 (Cristofori), and Marchi et al. US 5,496,807 (Marchi).

Claims 29-36 are drawn to a method of treating diabetic nephropathy comprising administering at least 200 mg/day of sulodexide or a pharmaceutically acceptable salt.

Baggio teaches sulodexide as preventing and curing the nephropathy caused by diabetes by fighting against the phenomena that cause the alterations of the renal structure and function (column 1, lines 59-65). Baggio further teaches dosages of up to

500 mg of sulodexide for the treatment of renal insufficiency [diabetic nephropathy caused by renal insufficiency] (column 2, lines 36-44).

Baggio differs from the instantly claimed invention in that Baggio: 1) does not teach oral administration of the sulodexide composition; and 2) does not teach administration of greater than 500 mg of sulodexide. Although Baggio does not teach administration of 525 mg of sulodexide, the difference between the administrations of 500 mg compared to 525 mg of sulodexide is not seen to add patentability over the prior art. A *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Cristofori and Marchi teach oral administration of sulodexide.

Cristofori discloses pharmaceutical compositions for oral use comprising sulodexide (column 3, lines 34-43). The composition may be in the form of tablets or capsules (hard or soft) (column 4, lines 12-34).

Marchi discloses pharmaceutical compositions of sulodexide for the treatment of diabetic nephropathy. The composition may be in the form of tablets, capsules, granulates, or syrups for oral administration (column 3, lines 1-5).

It indeed would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Cristofori, Baggio, and Marchi to arrive at the instant invention as Baggio teaches dosages of up to 500 mg of sulodexide, which is taught in the prior art as being suitable for oral administration, for the treatment of renal insufficiency [diabetic nephropathy caused by renal insufficiency]. One would have

been motivated to do so in order to provide effective treatment since factors such as the extent of the illness and body weight of the patient could render conventional compositions ineffective. Thus, the instant invention is seen to be within the purview of the skilled artisan.

Rejections of Record Set Forth in Office Action dated June 27, 2002

5. Claims 1-27 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cristofori et al. US 5,252,339 (Cristofori), Marchi et al. US 5,496,807 (Marchi), and Baggio et al. US 5,686,432 (Baggio).

Claims 1-25 are drawn to pharmaceutical compositions comprising from about 100 mg to about 1000 mg of sulodexide. Claims 26-27 are drawn to a method of treating diabetic nephropathy comprising administering 100 to 1000 mg/day of sulodexide or a pharmaceutically acceptable salt.

Cristofori discloses pharmaceutical compositions for oral use comprising sulodexide (column 3, lines 34-43). Therapeutic dosages contain 25 to 250 mg sulodexide (column 3, lines 20-22). The composition may be in the form of tablets or capsules (hard or soft) (column 4, lines 12-34).

Cristofori does not teach dosages of sulodexide greater than 250 mg. Cristofori does not teach a controlled-release composition. Cristofori does not disclose the treatment of diabetic nephropathy.

Baggio teaches dosages of up to 500 mg of sulodexide (column 2, lines 36-44). Marchi teaches the treatment of diabetic nephropathy by administering sulodexide

(Abstract). Marchi also teaches the use of controlled-released compositions (column 3, lines 1-5).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Cristofori, Baggio, and Marchi to arrive at the instant invention. One of ordinary skill in the art would aware of methods to increase the concentration of an active agent in order to obtain a desired effect. It would have been obvious to use the invention of Cristofori for the treatment of diabetic nephropathy since Marchi teaches compositions of sulodexide for the same purpose. Marchi also teaches the incorporation of the sulodexide compositions into controlled-release formulations. One would have been motivated to do so in order to provide effective treatment since factors such as the extent of the illness and body weight of the patient could render conventional compositions ineffective. Thus, the instant invention is seen to be within the purview of the skilled artisan.

Response to Arguments

6. Applicant's arguments filed June 17, 2003 have been fully considered but they are not persuasive.

Applicant argues that: 1) Cristofori does not teach or suggest the administration of sulodexide for the treatment of diabetic nephropathy; 2) Marchi does not teach treating diabetic nephropathy by administering more than 150 mg sulodexide per day; 3) Baggio does not teach the use of sulodexide for preventing and curing diabetic nephropathy; and 4) one skilled in the art would not take Baggio as a teaching that high

dosages of sulodexide can be administered orally. In response to applicant's assertion that the examiner has failed to establish a *prima facie* case of obviousness, the examiner respectfully disagrees.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Marchi teaches pharmaceutical compositions of sulodexide for the treatment of diabetic nephropathy. Contrary to applicant's assertion, Baggio does indeed teach that diabetic nephropathy is treated using sulodexide. Column 1, lines 59-65, states:

> "The ability of the sulodexide, a glycosaminoglycan of natural origin made by a heparin fraction having a low anticoagulant activity and by a dermatan fraction, of preventing and curing the nephropathy caused by the diabetes, by fighting against the phenomena that cause the alterations of the renal structure and function has been shown in the European Patent Publication EP 0624374."

The fact that passage references another publication for further details of the treatment regimen does not negate what Baggio explicitly teaches. Based on the teaching of Baggio and Marchi, it would have indeed been obvious to one of ordinary skill in the art at the time of the invention that sulodexide is suitable for the treatment of diabetic nephropathy.

Marchi further teaches that the sulodexide composition may be in the form of tablets, capsules, granulates, or syrups for oral administration (column 3, lines 1-5). The difficulty of finding oral pharmaceutical formulations containing glycosaminoglycans endowed with better bioavailability was noted by Cristofori (column 2, lines 22-38); however, Cristofori teaches a pharmaceutical composition for oral use in unit dosage form which comprises 25-500 mgs by weight of a glycosaminoglycan, wherein said glycosaminoglycan is sulodexide (Claim 1). In the absence of some proof of a secondary nature to obviate the rejection as set forth in the Office Action dated December 17, 2002, or of some specific limitations which would tip the scale of patentability in the favor of the instantly claimed invention, it would have been obvious to one of ordinary skill in this art at the time of the invention to treat a patient with diabetic nephropathy comprising orally administering 200-525 mg sulodexide per day.

Conclusion

7. Claims 26-27 and 29-36 are pending. Claims 26-27 and 29-36 are rejected. No claims are allowed.

8. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued

examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

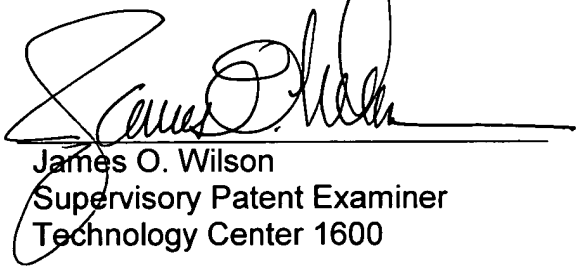
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Patrick T. Lewis, PhD
Examiner
Art Unit 1623

James O. Wilson
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ptl
September 3, 2003